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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,610	09/16/2003	Charles Wilson	23239-538 (ARC-38)	5499

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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	PAPER NUMBER
1648	
MAIL DATE	DELIVERY MODE
11/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/664,610	WILSON ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *127-137* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *127-137* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 15 October 2009 has been entered.

DETAILED ACTION

This Office Action is in response to the amendment filed 15 October 2009.

Claims 1-126 have been cancelled.

Claims 127, 132, 136 and 137 have been amended.

Claims 127-137 are pending and currently examined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

WITHDRAWN REJECTIONS

The rejection of claims 127-130, 133, 136 and 137 under 35 U.S.C. §103(a) as being obvious over Sullenger *et al*. (US 2003/0083294 A1, filed 25 May 2001) is **withdrawn** in response to Applicants' amendment.

The rejection of claims 131 and 132 under 35 U.S.C. §103(a) as being obvious over Sullenger *et al*. (US 2003/0083294 A1, filed 25 May 2001) in view of Griffin *et al*. (US 5,756,291, patented 26 May 1998) **is withdrawn** in response to Applicants' amendment.

The rejection of claims 133-135 under 35 U.S.C. §103(a) as being obvious over Sullenger *et al*. (US 2003/0083294 A1, filed 25 May 2001) in view of Gold *et al*. (US 5,763,173, patented 9 June 1998, No. A28 in IDS filed 22 May 2006) **is withdrawn** in response to Applicants' amendment.

Response to Arguments

Applicant's arguments have been considered but are moot in view of the new grounds of rejection.

NEW REJECTIONS NECESSITATED BY AMENDMENT

Claims 127-133, 136 and 137 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cubicciotti *et al*. (US 6,287,765, B1, patented 11 September 2001, hereinafter "Cubicciotti").

The instant claims are directed to a method for identifying an aptamer regulator comprising:

(a) providing a target and a target partner that do not bind to each other;

(b) contacting a mixture of nucleic acids with a target and a target partner under conditions that disfavor efficient binding between the target and the target partner;

(b) partitioning nucleic acids bound to a target-target partner (T/TP) complex from unbound nucleic acids; and

(c) retaining the nucleic acids bound to the T/TP complex, thereby identifying an aptamer that binds to a target, wherein binding of the aptamer to the target increases the binding affinity of the target for the target partner relative to when the target is not bound by the aptamer.

The claim limitation of binding between a "target" and "target partner" reads on members of a recognition pair, functional coupling between nonolignonucleotide molecules, multimolecular devices, ligand-receptor binding, and prodrug-target binding. The claim limitation of "aptamer regulator" reads on any non-naturally occurring nucleotides, defined sequence segments, synthetic oligonucleotides or nucleic acids.

Cubicciotti discloses various methods of selecting apatmeric and catalytic nucleotides for assembly of functionally coupled multimolecular devices (col. 11, lines 46-54) and of selecting synthetic heteropolymers (Abstract), aptameric multimolecular complex (col. 14, lines 30-37) or nucleotide templates (col. 3, lines 23-57) for binding two different nonoligonucleotide molecules (col. 14, lines 30-37) such as a ligand-

receptor complex (col. 163, 5-49), which includes selection from a highly diverse nucleic acid library (meets the limitation in claim 129), isolation (including the steps of "partitioning" and "retaining" in claim 127c and 127d), characterization, and sequencing of the individual selected nucleotide as well as screening (meets the limitation in claim 137) for a defined sequence segment capable of binding a complex comprising two molecules (col. 162, lines 63-67). Cubicciotti also discloses that the mixture of nucleotides can be designed to specifically bind nonoligonucleotide target molecules with high affinity (claim 128 limitation) (col. 3, lines 27-30). Cubicciotti further discloses that a selection method further comprises immobilized selected target molecule (col. 255, lines 37-38) or immobilized ligand of a ligand-receptor complex (col. 163, line 29), removing the retained nucleic acids from the target molecule (col. 255, lines 41-42) and amplifying the retained nucleic acids (limitation in claim 136) (col. 255, line 52; and col. 163, lines 47-48).

Although Cubicciotti does not explicitly disclose that the target and target partner do not bind to each other in the absence of an aptamer (claims 127a limitation) and that the conditions disfavor binding between the target and the target partner (claim 127b limitation), Cubicciotti clearly suggests combining the selection of a first aptamer binding to a first nonoligonucleotide molecule, which can be the claimed target, and the selection of a second aptamer binding to a second nonoligonucleotide molecule, which can be the claimed target partner, for the purpose of assembling the two molecules in close distance for coupling function. The disclosed strategy of nucleotide-directed molecular assembly involves the selection of a synthetic heteropolymer comprising a

synthetic aptamer attached to a defined sequence which may comprise an aptamer (col. 6, lines 29-37) so that the heteropolymer can recognize a first and a second nonoligonucleotide molecule nonoligonucleotide molecule (col. 6, lines 7-28). This synthetic heteropolymer serves as a template for assembling two specific recognition paired partners within functional coupling distance (col. 4, lines 33-67). It is immediately apparent to one skilled in the art that this synthetic heteropolymer, especially in the application of multimolecular drug delivery system which delivers prodrugs to receptor-targets (col. 11, lines 6-15), would meet the limitation of an aptamer regulator that binds to a target and a target partner under conditions disfavoring binding between the target and target partner.

It would be obvious to one skilled in the art at the time of invention to select for a synthetic heteropolymer, such as the claimed aptamer regulator, from a diverse pool of nucleic acids comprising a first aptamer that recognizes a target and a second aptamer that recognizes a target partner, under conditions that the target and target partner do not bind each other in the absence of an aptamer regulator, with the predictable results of the aptamer regulator binding to both the target and target partner to form a multi-molecular complex. There would have been a reasonable expectation of success because Cubicciotti specifically discloses an “aptameric multimolecular complex” that is a synthetic heteropolymer comprising two different aptamer molecules directly attached or conjugated to one another or indirectly attached via a linker that joins the aptamers to form a discrete heteropolymeric structure capable of specifically recognizing two different nonoligonucleotide molecules (col. 14, lines 30-37), given Cubicciotti's

suggestion of selecting a synthetic heteropolymer under conditions of variable and increasing stringency and/or selection pressure (col. 32, lines 60-61) from an experimental or willfully designed pool, mixture, population, library or assortment of sequences, preferably a diverse pool, mixture, population, library or assortment (col. 85, lines 47-51), wherein a first library can be coupled to second library to evolve a mapping library of nucleotides that recognize the selected population of nonnucleotide molecules (col. 106, lines 24-67), and given Cubicciotti's suggestion of detecting the signals from functional coupling between preselected recognition partners (col. 139, lines 15-45) for screening for nucleotide templates that bind or attach the recognition partners.

It would be obvious to one skilled in the art at the time of invention to modify the Cubicciotti method to immobilize the target partner (limitation in claim 130) instead of the target and to remove the retained nucleic acids from the T/TP complex (limitation in claim 133) instead of from the target for the ease of selection, isolation and screening of desired aptamers binding together the target and target partner. One skilled in the art would obtain predictable results of immobilizing the aptamer-target complex because there is a finite number of solutions, which is immobilizing either of the two members of the target complex, the target or the target partner.

Cubicciotti further suggests a step of counter-selection (which is the same as negative selection) against a selected ligand and receptor before the selection for identifying synthetic oligonucleotides that bind to a ligand-receptor complex (col. 163, lines 3-4). It would be obvious to one skilled in the art at the time of invention to modify the Cubicciotti method to so as to include a further step of negative selection (limitations

in claims 131 and 132) of partitioning target partner-bound nucleic acids from unbound nucleic acids and retaining unbound nucleic acids prior to the selection for aptameric multimolecular complex (which is functionally the same as the claimed aptamer regulator) binding two different nonoligonucleotide molecules (which include the claimed target and target partner). One having ordinary skill in the art would have been motivated to make such a modification to remove the undesired nucleic acids that bind only target partners to quantitatively titrate the stringencies of the pool or library of nucleic acids, as suggested by Cubicciotti (col. 160, lines 46-67), in order to increase the efficiency of the selection method. There would have been a reasonable expectation of success, given the example of a nucleic acid library counterselected against a selected ligand and receptor and then selected for defined sequence segments capable of specifically binding the bound ligand-receptor complex in such a manner that the selected defined sequence segment binds neither the labeled aptamer ligand nor the free target receptor (col. 163, lines 1-49), as taught by Cubicciotti. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 134 is rejected under 35 U.S.C. §103(a) as being unpatentable over Cubicciotti *et al*. (US 6,287,765 B1, patented 11 September 2001, hereinafter "Cubicciotti") in view of Gallivan *et al*. (US 2003/0064931 A1, effectively filed on 28 September 2001, hereinafter "Gallivan").

The instant invention further limits the step of removing the retained nucleic acids from the target-target partner complex by eluting the nucleic acids with free excess target.

The disclosure of Cubicciotti is set forth above. Cubicciotti does not specifically disclose the approach of eluting the nucleic acids with excess free target.

Gallivan discloses eluting the bound nucleic acids with excess free target (p. 5, [0043]) in a method of partitioning RNA molecules bound to a target molecule immobilized to a resin in a chromatography column.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the selection method disclosed by Cubicciotti so as to further include the step of eluting the nucleic acids with free excess target, as taught by Gallivan, with a reasonable expectation of success because this elution technique is a routine procedure known in the art of aptamer selection. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claim 135 is rejected under 35 U.S.C. §103(a) as being unpatentable over Cubicciotti *et al*. (US 6,287,765 B1, patented 11 September 2001, hereinafter "Cubicciotti") in view of Gold *et al*. (U.S. Patent No. 5,763,173, patented 9 June 1998, No. A28 in IDS filed 22 May 2006, hereinafter '173).

The instant invention further limits the step of removing the retained nucleic acids from the target-target partner complex by eluting the nucleic acids with an agonist competitor to the target.

The disclosure of Cubicciotti is set forth above. Cubicciotti does not specifically disclose the approach of eluting the nucleic acids with an agonist competitor to the target.

Gold patent '173 discloses the specific procedure of eluting bound DNA aptamers with tRNA (column 9, lines 15- 26). The tRNA is a competitor to the target DNA polymerase (col. 9, line 17).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the selection method disclosed by Cubicciotti so as to further include the step of eluting the nucleic acids with an agonist competitor to the target, as taught by the Gold patent, with a reasonable expectation of success because with a reasonable expectation of success because this elution technique is a routine procedure known in the art of aptamer selection. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648

/Jeffrey S. Parkin/
Primary Examiner, Art Unit 1648

18 November 2009